CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-903

STATISTICAL REVIEW(S)

HFD 530/Crescenzi

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Statistical Review and Evaluation

NDA#:	20-903
APPLICANT:	Schering Corporation
NAME OF DRUG:	Rebetol™ (ribavirin) Capsules
INDICATION:	Treatment of Chronic Hepatitis C
DOCUMENTS REVIEWED:	3.1, 3.2, 3.169-3.294, CANDA (12/03/97)
MEDICAL INPUT:	HFD-530: R. Fleischer, PA. C, MPH
	HFD-530: T. Nguyen, M.D.

A. Background

This NDA contains four pivotal, independent, multicenter trials (2 U.S. and 2 International) to support the proposed indication for the treatment of chronic hepatitis C. Efficacy was evaluated based upon C95-144 (U.S. trial) and I95-145 (International trial) which were two identical studies for patients with chronic hepatitis C who responded to initial treatment of interferon and relapsed thereafter. The summary of safety was based on the above two studies reviewed for efficacy as well as a Phase I study (in patients with chronic hepatitis C), a Phase II study (in patients with chronic hepatitis C not previously treated) and the two ongoing Phase III studies. In this review, only studies C95-144 and I95-145 will be reported.

Protocols C95-144 and 195-145

Title: "Intron® A Monotherapy vs. Intron® A+Ribavirin for Treatment of Relapse in Patients with Chronic Hepatitis C "

Both protocols were double-blind, placebo-controlled, multicenter, randomized, parallel group trials comparing two treatment strategies in patients with compensated chronic hepatitis C who responded to one or two courses of alpha interferon and who had relapsed (based upon ALT > ULN) after the most recent course of alpha interferon therapy. Approximately one hundred and fifty (150) patients on each protocol were to be enrolled at about 15 study sites with an estimated 10 patients at each site. Patients were to be equally randomized using a centralized randomization procedure described by Pocock and Simon (1975) to receive either Intron A + placebo for 24 weeks or Intron A + ribavirin for 24 weeks. This randomization procedure was designed to balance the treatment groups with respect to the following baseline characteristics:

- pretreatment liver histology (cirrhosis or no cirrhosis);
- serum HCV RNA/qPCR status (HCV RNA/qPCR ≤2,000,000 copies/mL or >2,000,000 copies/mL); and
- HCV genotype (I or other).

Patients had clinical visits at weeks 1, 2, 4, 6, 8, 12, 16, 20 and 24 during treatment and at weeks 4, 8, 12 and 24 during the follow-up period. Serum HCV RNA/qPCR was to be evaluated at weeks 4, 12 and 24 during treatment and at weeks 12 and 24 following the end of therapy. A liver biopsy was to be done at baseline and after 24 weeks of treatment free follow-up.

The primary efficacy endpoint for this study is the overall response defined below. The primary objective was to compare Intron A + Ribavirin with Intron A + Placebo at 24 weeks of follow-up (i.e., study week 48) with respect to overall response. Sustained response at 24 weeks of follow-up was also of interest.

Responder: a patient was classified as a virologic responder at a given time point if the HCV RNA was below the reported lower limit of quantification (LOQ) of the serum PCR assay at that time point.

Sustained responder: a patient was a sustained responder if his/her serum HCV RNA was below LOQ at the end of follow-up (i.e., study week 48). Specifically, a sustained responder completed at least 141 days of follow-up and had no HCV RNA above LOQ between 141 and 196 days of follow-up. If a patient had no HCV RNA evaluations between 141 and 196 days of follow-up, the first HCV RNA evaluation after 196 days of follow-up had to be below LOQ.

Overall response: each patient's overall response status was classified as: overall responder, overall non-responder, or missing. A patient was classified as an overall responder if he/she was a sustained virologic responder and his/her post-treatment liver biopsy score (Knodell score components I, II and III) improved by 2 or more units relative to the pre-treatment score. A patient was an overall non-responder if he/she was not a sustained virologic responder and/or the post-treatment liver score did not improve by 2 or more units relative to the pre-treatment score. Finally, a patient's overall response was classified as missing if he/she was a sustained virologic responder but the liver score could not be determined.

B. Results of the Applicant's Analyses

Study C95-144

Study C95-144 started in April, 1996 and ended in June, 1997. One-hundred and fifty-four (154) were randomized and 153 treated: 77 treated with Intron A plus ribarivin and 76 treated with Intron A plus placebo.

The primary efficacy analysis of the overall response rate was based on the intent-to-treat approach using a logistic regression model with main effects due to treatment, genotype, presence of cirrhosis, and baseline HCV RNA. In this analysis, subjects with missing HCV RNA evaluations were regarded as non-sustained HCV RNA responders and therefore non-overall responders. However, for subjects whose HCV RNA levels were below LOQ at Week 48 and whose biopsy changes were missing, the missing biopsy was assumed to be non-informative in the sense that, for a given combination of covariates, these subjects had the same chance of being biopsy responders as those subjects with biopsy scores available. For this analysis, the main effects were estimated by a maximum likelihood-based method (MLE). In this analysis, the sustained response was also modeled by the same logistic regression procedure which incorporated the same independent variables as the overall response analysis. Comparability of the treatment groups at baseline was assessed using Fisher's exact test.

Baseline Characteristics

A total of 153 patients were treated in the study with median age 43 years (range from 28 to 67). The two treatment groups were similar at baseline in demographic characteristics. The disease profile in both treatment groups was similar.